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Evidence-Based Use of Levothyroxine/Liothyronine Combinations in Treating Hypothyroidism: A Consensus Document

Jacqueline Jonklaas¹, Antonio C Bianco², Anne R Cappola³, Francesco S Celi⁴, Eric Fliers⁵, Heike Heuer⁶, Elizabeth A McAninch⁷, Lars C Moeller⁶, Birte Nygaard⁸, Anna M Sawka⁹, Torquil Watt¹⁰, Colin M Dayan¹¹

Affiliations

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Affiliations

- 1 Division of Endocrinology, Georgetown University, Washington, District of Columbia, USA.
- 2 Section of Adult and Pediatric Endocrinology and Metabolism, University of Chicago, Chicago, Illinois, USA.
- 3 Division of Endocrinology, Diabetes, and Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
- 4 Division of Endocrinology, Diabetes and Metabolism, Virginia Commonwealth University, Richmond, Virginia, USA.
- 5 Department of Endocrinology and Metabolism, Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam University Medical Center, Netherlands.
- 6 Department of Endocrinology, Diabetes and Metabolism, University Duisburg-Essen, Essen, Germany.
- 7 Division of Endocrinology, Rush University, Chicago, Illinois, USA.
- 8 Center for Endocrinology and Metabolism, Department Internal Medicine, Herlev and Gentofte Hospitals, Herlev, Denmark.
- 9 Division of Endocrinology, University Health Network and University of Toronto, Toronto, Canada.
- 10 Department of Endocrinology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark.
- 11 Thyroid Research Group, School of Medicine, Cardiff University, Cardiff, United Kingdom.

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Abstract

Background: Fourteen clinical trials have not shown a consistent benefit of combination therapy with levothyroxine (LT4) and liothyronine (LT3). Despite the publication of these trials, combination therapy is widely used and patients reporting benefit continue to generate patient and physician interest in this area. Recent scientific developments may provide insight into this inconsistency and guide future studies. **Methods:** The American Thyroid Association (ATA), British Thyroid Association (BTA), and European Thyroid Association (ETA) held a joint conference on November 3, 2019 (live-streamed between Chicago and London) to review new basic science and clinical evidence regarding combination therapy with presentations and input from 12 content experts. After the presentations, the material was synthesized and used to develop Summary Statements of the current state of knowledge. After review and revision of the material and Summary Statements, there was agreement that there was equipoise for a new clinical trial of combination therapy. Consensus Statements encapsulating the implications of the material discussed with respect to the design of future clinical

trials of LT4/LT3 combination therapy were generated. Authors voted upon the Consensus Statements. Iterative changes were made in several rounds of voting and after comments from ATA/BTA/ETA members. **Results:** Of 34 Consensus Statements available for voting, 28 received at least 75% agreement, with 13 receiving 100% agreement. Those with 100% agreement included studies being powered to study the effect of deiodinase and thyroid hormone transporter polymorphisms on study outcomes, inclusion of patients dissatisfied with their current therapy and requiring at least 1.2 µg/kg of LT4 daily, use of twice daily LT3 or preferably a slow-release preparation if available, use of patient-reported outcomes as a primary outcome (measured by a tool with both relevant content validity and responsiveness) and patient preference as a secondary outcome, and utilization of a randomized placebo-controlled adequately powered double-blinded parallel design. The remaining statements are presented as potential additional considerations. **Discussion:** This article summarizes the areas discussed and presents Consensus Statements to guide development of future clinical trials of LT4/LT3 combination therapy. The results of such redesigned trials are expected to be of benefit to patients and of value to inform future thyroid hormone replacement clinical practice guidelines treatment recommendations.

Keywords: clinical trial; combination therapy; hypothyroidism; levothyroxine; liothyronine; patient-reported outcomes.

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